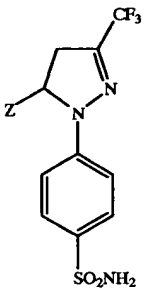
concentrations in a solution containing 100 mM Tris-HCl, pH7.8, 500 μM phenol and hematin for 90 to 120 minutes at room temperature (24° C.). In controls, equal volumes of DMSO without drug were added to the incubation mixture. After incubation for 90–120 minutes, [1-^{14}C] arachidonic acid (50 μM, 51 mCi/mmol) (DuPont NEN) was added and incubated at 37° C. for 2 minutes. The reaction was terminated by extraction with 1 ml of ethyl acetate. The ethyl acetate layer was transferred into a fresh tube and evaporated to dryness in a Speedvac vacuum dryer. The contents of the tubes were reconstituted in 20 ml of ethyl acetate and spotted on a TLC plate (J. T. Baker, Phillipsburg, N.J.) and developed in a mobile phase containing chloroform/methanol (95:5) at4° C. Radiolabeled prostanoid compounds (the products of COX enzymatic reaction with radiolabeled arachidonic acid substrate) were quantitated with a radioactivity scanner (Fuji, Phosphorimager). The percentage of total products observed at different inhibitor concentrations was divided by the percentage of the products observed for protein samples pre incubated for the same time with DMSO. The results are shown in Table 4. The Example 1 and 2 compounds are more than one thousand times more active in inhibiting COX-2 compared to COX-1.

TABLE 4

Inhibition of Cyclooxygenase Activity



		IC_{50}(μM)	
Ex.	Z	COX-2	COX-2
1	C_6H_5	0.10	<100
24	3-indolyl	0.078	<100

Soft Agar Assay

The Example 1 and 24 compounds were compared to the COX-2 inhibitor celecoxib in inhibiting the growth of DLD-1 cells in soft agar. DLD-1 cells are human colorectal carcinoma cells that overexpress COX-2. DLD-1 cells grow in soft agar and form tumors in nude mice. The soft agar assay was performed as follows. A layer of bottom agar (8% noble agar) was placed onto 60 mm^2 tissue culture dishes. The tumor cells were trypsinized from normal growth flasks while in exponential growth. The cells were counted by using a hemacytometer and 1.0×10^5 cells were placed into the top agar mixture containing growth medium, 4% noble agar and various concentrations of drugs. The concentration range was normally between 10 μM to 75 μM. The cells were not refed during the assay system; therefore, the cells were treated with one dose of the agents. The plates were stained 20 days later with a 0.05% (w/v) nitroblue tetrazolium solution (which stains only viable cells) for 48 hours. The results are shown in FIG. 1, the y-axis being the percent of cell colonies remaining in comparison to untreated control cells. Even at the highest concentration tested, celecoxib obtained only about partial inhibition, compared to 100% for the compounds of the invention.

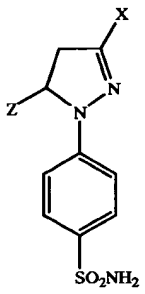
All references cited herein are incorporated herein by reference.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, ratherthan to the foregoing specification, as indication the scope of the invention.

What is claimed is:

1. A compound of the formula:

(I)



wherein:

is selected from the group consisting of trihalomethyl and C_1–C_6 alkyl;

Z is selected from the group consisting of substituted and unsubstituted aryl other than substituted and unsubstituted phenyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Z is selected from the group consisting of substituted and unsubstituted heteroaryl; or a pharmaceutically acceptable salt thereof.

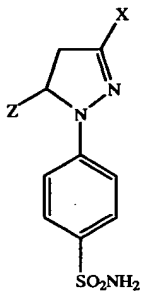
3. A compound according to claim 2 wherein Z is selected from the group consisting of substituted and unsubstituted indolyl, furyl, thienyl, pyridyl, benzofuryl, benzothienyl, imidazolyl, pyrazolyl, thiazolyl, benzothazolyl, quinolinyl, and 4-(2-benzyloxazolyl); or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 wherein Z is 3-indolyl; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 wherein X is trifluoromethyl.

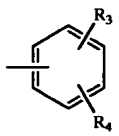
6. A compound of the formula:

(I)



wherein:

X is a group of formula II:



(II)

wherein:

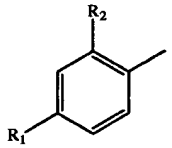
R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and unsubstituted aryl, and when Z is heteroaryl, it is selected from the group consisting of substituted and unsubstituted pyridyl, furyl, indolyl, benzothienyl, benzofuryl, imidazolyl, pyrazolyl, 2-thiazolyl, quinolinyl and 4-(2-benzyloxazolyl); or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **6** wherein Z is selected from the group consisting of unsubstituted phenyl; and mono-, di- and tri-substituted phenyl.

8. A compound according to claim **7** wherein Z is phenyl substituted with one or more of halogen, hydroxyl, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or carboxy; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim **10** wherein Z is the group



wherin R_1 an R_2areindependently selected from the group consisting of hydrogen, fluorine, bromine, chlorine, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl and nitro; or a pharmaceutically acceptable salt thereof.

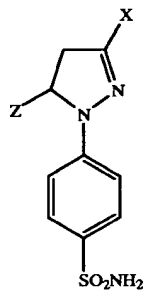
10. A compound according to claim **6** wherein Z is substituted or unsubstituted indolyl, furyl, pyridyl or benzofuryl; or a pharmaceutically acceptable salt thereof.

11. A compound according to claim **10** wherein Z is substituted or unsubstituted 3-indolyl; or a pharmaceutically acceptable salt thereof.

12. The compound according to claim **1** which is 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-(3-indolyl)-2-pyrazoline; or a pharmaceutically acceptable salt thereof.

13. A compound of the formula:

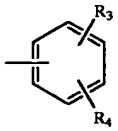
(I)



wherein:

X is a group of formula II:

(II)



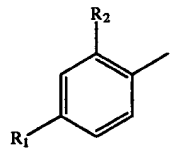
wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen, C_1–C_6 alkyl and C_1–C_6 alkoxy;

Z is selected from the group consisting of phenyl; phenyl monosubstituted with halogen, hydroxyl, nitro or carboxy; disubstituted phenyl; trisubstituted phenyl; and heteroaryl selected from the group consisting of substituted and unsubstituted pyridyl, furyl, indolyl, benzothienyl, benzofuryl, imidazolyl, pyrazolyl, 2-thiazolyl, quinolinyl and 4-(2-benzyloxazolyl); or a pharmaceutically acceptable salt thereof.

14. A compound according to claim **13** wherein Z is the group

(III)



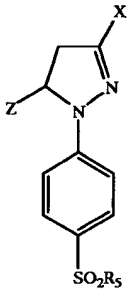
wherein R_1 and R_2 are independently selected from the group consisting of fluorine, bromine, chlorine, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl and nitro; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim **13** wherein Z is substituted or unsubstituted indolyl, furyl, pyridyl or benzofuryl; or a pharmaceutically acceptable salt thereof.

16. A compound according to claim **15** wherein Z is substituted or unsubstituted 3-indolyl; or a pharmaceutically acceptable salt thereof.

17. A compound of the formula V:

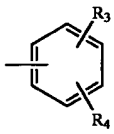
(V)



wherein:

X is selected from the group consisting of trihalomethyl, C_1–C_6 alkyl, and a group of formula II:

(II)



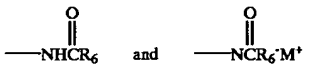
wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1–C_6 alkyl;

C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is substituted or unsubstituted heteroaryl; and

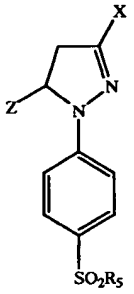
R_5 is selected from the group consisting of



wherein R_6 is C_1–C_6 alkyl and M is Na, K or Li; or a pharmaceutically acceptable salt thereof.

18. A compound of the formula V:

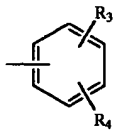
(V)



wherein:

X is a group of formula II:

(II)



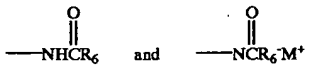
wherein:

R_3 and R_4 are independently selec ted f rom th e group consisting of hydrogen; halogen; hydroxyl; nitro; C_1–C_6, alkyl;

C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and unsubstituted aryl; and

R_5 is selected from the group consisting of



wherein R_6 is C_1–C_6 alkyl and M is Na, K or Li or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to claim 17 or 18, or a pharmaceutically acceptable salt thereof.

20. A method for treating a cyclooxygenase-mediated disorder comprising administering to a patient in need of such treatment an effective amount of a compound according to claim 17 or 18, or a pharmaceutically acceptable salt thereof.

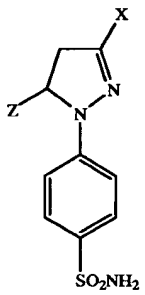
21. A method for treating inflammation or an inflammation-mediated disorder comprising administering to a subject in need of such treatment an effective amount of a compound according to claim 17 or 18, or a pharmaceutically acceptable salt thereof.

22. A method for treating a neoplasia comprising administering to a subject in need of such treatment an effective amount of a compound according to claim 17 or 18, or a pharmaceutically acceptable salt thereof.

23. A method for treating an angiogenesis-mediated disorder administering to a subject in need of such treatment an effective amount of a compound according to claim 17 or 18, or a pharmaceutically acceptable salt thereof.

24. A method for producing a compound of formula I

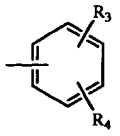
(I)



wherein:

the group X is selected from the group consisting of trihalomethyl, C_1–C_6 alkyl, and a radical of formula II:

(II)



wherein:

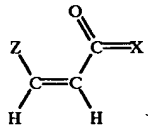
wherein R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano; and

Z is selected from the group consisting of substituted and unsubstituted aryl, other than substituted and unsubstituted phenyl;

the method comprising:

(a) reacting a compound of the formula IV

(IV)



wherein X and Z are so defined;

with 4-sulfamyl phenyl hydrazine or salt thereof; and

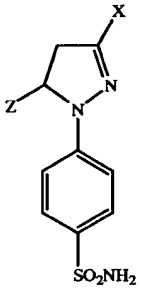
(b) isolating a compound according to formula I from the reaction products.

25. A method according to claim **24** wherein Z is substituted or unsubstituted heteroaryl.

26. A method according to claim **24** wherein X is a radical of formula II.

27. A method for producing a compound of formula I

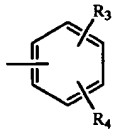
(I)



wherein

the group X is a radical of formula II:

(II)



wherein:

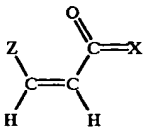
R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, carboxy, C_1–C_6 trihaloalkyl, and cyano; and

Z is selected from the group consisting of substituted and unsubstituted aryl;

the method comprising:

(a) reacting a compound of the formula IV

(IV)



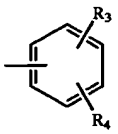
wherein X and Z are so defined;

with 4-sulfamyl phenyl hydrazine or salt thereof; and

(b) isolating a compound according to formula I from the reaction products.

28. A method according to claim **27** wherein the group X in the reactant compound of formula IV is a radical of formula II:

(II)



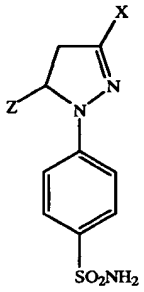
wherein:

wherein R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy; and carboxy.

29. An isolated optical isomer of a compound according to claim **17** or **18**, or a pharmaceutically acceptable salt thereof.

30. An isolated optical isomer of a compound of the formula:

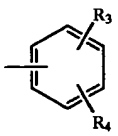
(I)



wherein:

X is selected from the group consisting of trihalomethyl, C_1–C_6 alkyl, and a group of formula II:

(II)



wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro;

C_1–C_6 alkyl; C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and unsubstituted aryl; or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to claim **1**.

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to claim **6**.

33. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to claim **13**.

34. A method for treating a cyclooxygenase-mediated disorder comprising administering to a patient in need of such treatment an effective amount of a compound according to claim **1**.

35. A method for treating a cyclooxygenase-mediated disorder comprising administering to a patient in need of such treatment an effective amount of a compound according to claim **6**.

36. A method for treating a cyclooxygenase-mediated disorder comprising administering to a patient in need of such treatment an effective amount of a compound according to claim **13**.

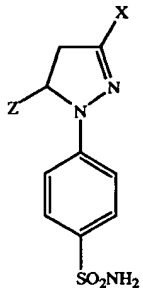
37. A method for treating inflammation or an inflamation-mediated disorder comprising administering to a subject in need of such treatment an effective amount of a compound according to claim **1**.

38. A method for treating inflammation or an inflamation-mediated disorder comprising administering to a subject in need of such treatment an effective amount of a compound according to claim **6**.

39. A method for treating inflammation or an inflamation-mediated disorder comprising administering to a subject in need of such treatment an effective amount of a compound according to claim **13**.

40. A method for treating a neoplasia comprising administering to a subject in need of such treatment an effective amount of a compound of the formula:

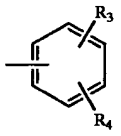
(I)



wherein:

X is selected from the group consisting of trihalomethyl, C_1–C_6 alkyl, and a group of formula II.

(II)



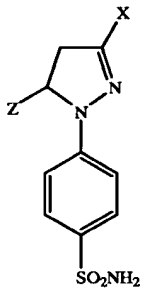
wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1–C_6 alkyl; C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and unsubstituted aryl; or a pharmaceutically acceptable salt thereof.

41. A method for treating an angiogenesis-mediated disorder administering to a subject in need of such treatment an effective amount of a compound of the formula:

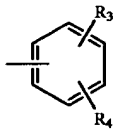
(I)



wherein:

X is selected from the group consisting of trihalomethyl, C_1–C_6 alkyl, and a group of formula II:

(II)



wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1–C_6 alkyl; C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and unsubstituted aryl; or a pharmaceutically acceptable salt thereof.

42. A method according to claim **40** or **41** wherein Z is selected from the group consisting of substituted and unsubstituted heteroaryl; or a pharmaceutically acceptable salt thereof.

43. A method according to claim **42** wherein Z is selected from the group consisting of substituted and unsubstituted indolyl, furyl, thienyl, pyridyl, benzofuryl, benzothienyl, imidazolyl, pyrazolyl, thiazolyl, benzothiazolyl, quinolinyl, and 4-(2-benzyloxazolyl); or a pharmaceutically acceptable salt thereof.

44. A method according to claim **43** wherein Z is substituted or unsubstituted 3-indolyl; or a pharmaceutically acceptable salt thereof.

45. A method according to claim 40 or 41 wherein X is trifluoromethyl.

46. A method according to claim 40 or 41 wherein X is a group according to formula II wherein R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1–C_6 alkyl; C_1–C_6 alkoxy; carboxy; C_1–C_6 trihaloalkyl; and cyano; or a pharmaceutically acceptable salt thereof.

47. A method according to claim 46 wherein Z is selected from the group consisting of unsubstituted phenyl; and mono-, di- and tri-substituted phenyl.

* * * * *